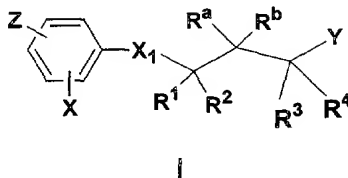


CLAIMS

We claim:

- 5 1. A compound of the formula



- 10 wherein X_1 is O, $S(O)_n$, $-\overset{R^5}{N}-$, $co-\overset{R^5}{N}-$, or $-CH_2-$, with the proviso that when X_1 is $-CH_2-$, R_1 and R_2 are only halogen.

n is 0, 1 or 2;

- 15 R^a and R^b when taken together form an oxo ($=O$) group, or R^a and R^b are each independently hydrogen, OH, $OCOR^9$, NH_2 , N_3 , $NHCOOR^9$, $NHCOCOR^9$, $NHSO_2R^9$ or F;

- 20 X is H, CF_3 , OCF_3 , halogen, C_1-C_7 alkyl, C_2-C_7 alkenyl, C_2-C_7 alkynyl or C_3-C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by $COOR^8$, CN, $C(O)NR^6R^7$, PO_3R^8 , SO_3R^8 , heterocyclic, OR^8 , SH, $S(O)_nR^9$, NR^6R^7 , $NH(CO)NR^6R^7$, $NH(CO)OR^9$, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from NR^6R^7 , OR^8 , $COOR^8$, SO_3R^8 , $OCOR^9$, PO_3R^8 , $C(O)NR^6R^7$ or heterocyclic;

25

R^1 and R^2 are each independently H, halogen, OR^9 , C_1-C_7 alkyl, C_2-C_7 alkynyl, C_2-C_7 alkynyl or C_3-C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or

cycloalkyl group being optionally substituted by COOR⁸, CN, C(O)NR⁶R⁷, PO₃R⁸, SO₃R⁸, heterocyclic, OR⁸, SH, S(O)_nR⁹, NR⁶R⁷, NH(CO)NR⁶R⁷, NH(CO)OR⁹, OC(O)OR⁹, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted with one or two groups independently selected from

5 NR⁶R⁷, OR⁸, COOR⁸, SO₃R⁸, OCOR⁹, PO₃R⁸, C(O)NR⁶R⁷ or heterocyclic;

R³, R⁴ and Y are each independently H, halogen, OR¹⁰, S(O)_nR¹⁰, C₁–C₇ alkyl, C₂–C₇ alkenyl, C₂–C₇ alkynyl or C₃–C₇ cycloalkyl, said alkyl,

10 alkenyl, alkynyl or cycloalkyl group being optionally substituted by COOR⁸, CN, C(O)NR⁶R⁷, PO₃R⁸, SO₃R⁸, heterocyclic, OR⁸, SH, S(O)_nR⁹, NR⁶R⁷, NH(CO)NR⁶R⁷, NH(CO)OR⁹, OC(O)OR⁹, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from NR⁶R⁷, OR⁸, COOR⁸, SO₃R⁸,

15 OCOR⁸, PO₃R⁸, C(O)NR⁶R⁷ or heterocyclic, with the proviso that not all of R³, R⁴ and Y may be the same halogen;

R⁵, R⁶ and R⁷ are each independently H, C₁–C₇ alkyl, C₂–C₇ alkenyl, C₂–C₇ alkynyl or C₃–C₇ cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl

20 group being optionally substituted by COOR⁸, CN, OR⁸, NR⁸R⁹, SO₃R⁸, PO₃R⁸, halogen, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from COOR⁸, SO₃R⁸, PO₃R⁸ or heterocyclic;

25 R⁸ is H, C₁–C₇ saturated straight chain alkyl or cycloalkyl;

R⁹ is same as R⁸ but is not hydrogen;

- R¹⁰ is C₁–C₇ alkyl, C₂–C₇ alkenyl, C₂–C₇ alkynyl or C₃–C₇ cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by COOR⁸, CN, C(O)NR⁶R⁷, PO₃R⁸, SO₃R⁸, heterocyclic, OR⁸, SH, S(O)_nR⁹, NR⁶R⁷, NH(CO)NR⁶R⁷, NH(CO)OR⁹, aryl or heteroaryl, said
- 5 aryl or heteroaryl being optionally substituted by one or two groups independently selected from NR⁶R⁷, OR⁸, COOR⁸, SO₃R⁸, OCOR⁸, PO₃R⁸, C(O)NR⁶R⁷ or heterocyclic;

Z is OR¹¹, S(O)_nR¹¹, NR¹¹R¹² or CHR¹¹R¹²;

10

R¹¹ and R¹² are each independently hydrogen, C₁–C₇ alkyl, C₂–C₇ alkenyl, C₂–C₇ alkynyl or C₃–C₇ cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by NR¹³R¹⁴, S(O)_nR¹³, OR¹³, with the proviso that both R¹¹ and R¹² may not be hydrogen;

15

R¹³ and R¹⁴ are each independently H, SiR¹⁵R¹⁶R¹⁷, C₁–C₇ alkyl, C₂–C₇ alkenyl, C₂–C₇ alkynyl, aryl or C₃–C₇ cycloalkyl, said alkyl, alkenyl, alkynyl, aryl or cycloalkyl group being optionally substituted by one to three groups independently selected from COOR⁸, OR⁸, Si R¹⁵R¹⁶R¹⁷, OR¹⁵, aryl, biaryl or heteroaryl, said aryl, biaryl or heteroaryl being

20 optionally substituted with one to three groups independently selected from halogen, CF₃, OR⁸, COOR⁸, NO₂, or CN;

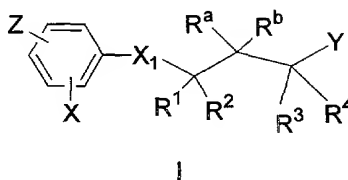
- R¹³ and R¹⁴ when taken together may form a 5 –7 membered
- 25 heterocyclic ring with one or more heteroatoms selected from O, N and S; said ring being optionally substituted by OR⁸, COOR⁸, or C(O)NR⁵R⁶;

R¹⁵, R¹⁶, R¹⁷ are each independently aryl, benzyl, benzhydryl, biaryl, heteroaryl, (C₁–C₆) alkyl–aryl or (C₁–C₆) alkyl–heteroaryl, said aryl radical

being optionally substituted by halogen, CF_3 , OR^8 , COOR^8 , NO_2 , CN , $\text{C}_1\text{-C}_7$ alkyl.

2. A compound of the formula

5



or a pharmaceutically acceptable salt thereof wherein

X_1 is O, S(O)_n , $\text{—}\overset{\text{R}^5}{\text{N}}\text{—}$, $\text{co—}\overset{\text{R}^5}{\text{N}}\text{—}$ or $\text{—CH}_2\text{—}$, with the proviso that when X_1 is $\text{—CH}_2\text{—}$, R_1 and R_2 are only halogen.

10

n is 0, 1 or 2;

R^a and R^b when taken together form an oxo ($=\text{O}$) group, or R^a and R^b are each independently hydrogen, OH, OCOR^9 , NH_2 , N_3 , NHCOOR^9 , NHCOCOR^9 , NHSO_2R^9 or F.

15

X is H, CF_3 , OCF_3 , halogen, $\text{C}_1\text{-C}_7$ alkyl, $\text{C}_2\text{-C}_7$ alkenyl, $\text{C}_2\text{-C}_7$ alkynyl or $\text{C}_3\text{-C}_7$ cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by COOR^8 , CN , $\text{C(O)NR}^6\text{R}^7$, PO_3R^8 , SO_3R^8 , heterocyclic, OR^8 , SH, $\text{S(O)}_n\text{R}^9$, NR^6R^7 , $\text{NH(CO)NR}^6\text{R}^7$, NH(CO)OR^9 , aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from NR^6R^7 , OR^8 , COOR^8 , SO_3R^8 , OCOR^9 , PO_3R^8 , $\text{C(O)NR}^6\text{R}^7$ or heterocyclic;

20

25

- R¹ and R² are each independently H, halogen, OR⁹, C₁–C₇ alkyl, C₂–C₇ alkenyl, C₂–C₇ alkenyl or C₃–C₇ cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by COOR⁸, CN, C(O)NR⁶R⁷, PO₃R⁸, SO₃R⁸, heterocyclic, OR⁸, SH, S(O)_nR⁹, NR⁶R⁷, NH(CO)NR⁶R⁷,
 5 NH(CO)OR⁹, OC(O)OR⁹, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted with one or two groups independently selected from NR⁶R⁷, OR⁸, COOR⁸, SO₃R⁸, OCOR⁹, PO₃R⁸, C(O)NR⁶R⁷ or heterocyclic;
- 10 R³, R⁴ and Y are each independently H, OR¹⁰, S(O)_nR¹⁰, C₁–C₇ alkyl, C₂–C₇ alkenyl, C₂–C₇ alkynyl or C₃–C₇ cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by COOR⁸, CN, C(O)NR⁶R⁷, PO₃R⁸, SO₃R⁸, heterocyclic, OR⁸, SH, S(O)_nR⁹, NR⁶R⁷, NH(CO)NR⁶R⁷, NH(CO)OR⁹, OC(O)OR⁹, aryl or heteroaryl, said aryl or
 15 heteroaryl being optionally substituted by one or two groups independently selected from NR⁶R⁷, OR⁸, COOR⁸, SO₃R⁸, OCOR⁸, PO₃R⁸, C(O)NR⁶R⁷ or heterocyclic;
- R⁵, R⁶ and R⁷ are each independently H, C₁–C₇ alkyl, C₂–C₇ alkenyl,
 20 C₂–C₇ alkynyl or C₃–C₇ cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by COOR⁸, CN, OR⁸, NR⁸R⁹, SO₃R⁸, PO₃R⁸, halogen, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from COOR⁸, SO₃R⁸, PO₃R⁸ or heterocyclic;
- 25 R⁸ is H, C₁–C₇ saturated straight chain alkyl or cycloalkyl, CF₃ or CH₂CF₃;

R⁹ is same as R⁸ but is not hydrogen;

R^{10} is C_1-C_7 alkyl, C_2-C_7 alkenyl, C_2-C_7 alkynyl or C_3-C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by $COOR^8$, CN , $C(O)NR^6R^7$, PO_3R^8 , SO_3R^8 , heterocyclic, OR^8 , SH ,

$S(O)_nR^9$, NR^6R^7 , $NH(CO)NR^6R^7$, $NH(CO)OR^9$, aryl or heteroaryl, said

- 5 aryl or heteroaryl being optionally substituted by one or two groups independently selected from NR^6R^7 , OR^8 , $COOR^8$, SO_3R^8 , $OCOR^8$, PO_3R^8 , $C(O)NR^6R^7$ or heterocyclic;

Z is OR^{11} , $S(O)_nR^{11}$, $NR^{11}R^{12}$ or $CHR^{11}R^{12}$;

10

R^{11} and R^{12} are each independently hydrogen, C_1-C_7 alkyl, C_2-C_7 alkenyl, C_2-C_7 alkynyl or C_3-C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by $NR^{13}R^{14}$, $S(O)_nR^{13}$, OR^{13} , with the proviso that both R^{11} and R^{12} may not be hydrogen;

15

R^{13} and R^{14} are each independently H , $SiR^{15}R^{16}R^{17}$, C_1-C_7 alkyl, C_2-C_7 alkenyl, C_2-C_7 alkynyl, aryl or C_3-C_7 cycloalkyl, said alkyl, alkenyl, alkynyl, aryl or cycloalkyl group being optionally substituted by one to three groups independently selected from $COOR^8$, OR^8 , $SiR^{15}R^{16}R^{17}$,

- 20 OR^{15} , aryl, biaryl or heteroaryl, said aryl, biaryl or heteroaryl being optionally substituted with one to three groups independently selected from halogen, CF_3 , OR^8 , $COOR^8$, NO_2 , or CN ;

R^{13} and R^{14} when taken together may form a 5 – 7 membered

- 25 heterocyclic ring with one or more heteroatoms selected from O , N and S ; said ring being optionally substituted by OR^8 , $COOR^8$, or $C(O)NR^5R^6$;

R^{15} , R^{16} , R^{17} are each independently aryl, benzyl, benzhydryl, biaryl, heteroaryl, (C_1-C_6) alkyl-aryl or (C_1-C_6) alkyl-heteroaryl, said aryl radical

being optionally substituted by halogen, CF_3 , OR^8 , COOR^8 , NO_2 , CN , or $\text{C}_1\text{--C}_7$ alkyl.

3. A compound of claim 2 wherein X_1 is O, or S(O)_n and Y is OR^{10} in
 5 which R^{10} is $\text{C}_1\text{--C}_7$ alkyl, $\text{C}_2\text{--C}_7$ alkenyl, $\text{C}_2\text{--C}_7$ alkynyl or $\text{C}_3\text{--C}_7$
 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally
 substituted by COOR^8 , CN , $\text{C(O)NR}^6\text{R}^7$, PO_3R^8 , SO_3R^8 , heterocyclic,
 OR^8 , SH , $\text{S(O)}_n\text{R}^9$, NR^6R^7 , $\text{NH(CO)NR}^6\text{R}^7$, NH(CO)OR^9 , aryl or
 heteroaryl, said aryl or heteroaryl being optionally substituted by one or
 10 two groups independently selected from NR^6R^7 , OR^8 , COOR^8 , SO_3R^8 ,
 OCOR^9 , PO_3R^8 , $\text{C(O)NR}^6\text{R}^7$ or heterocyclic, said R^6 , R^7 , R^8 and R^9
 substituents being defined as in claim 2.

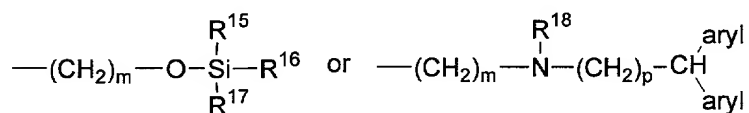
4. A compound of claim 3 in which R^a and R^b taken together
 15 represent an oxo ($=\text{O}$) group, or R^a and R^b are each independently
 hydrogen or OH.

5. A compound of claim 3 wherein R^a and R^b are each independently
 hydrogen, OCOR^9 , NH_2 , N_3 , NHCOOR^9 or NHCOCOR^9 in which R^9 is as
 20 defined in claim 2.

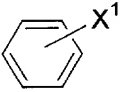
6. A compound of claim 4 wherein R^1 and R^2 are each independently
 halogen.

25 7. A compound of claim 3, 4, 5 or 6 in which

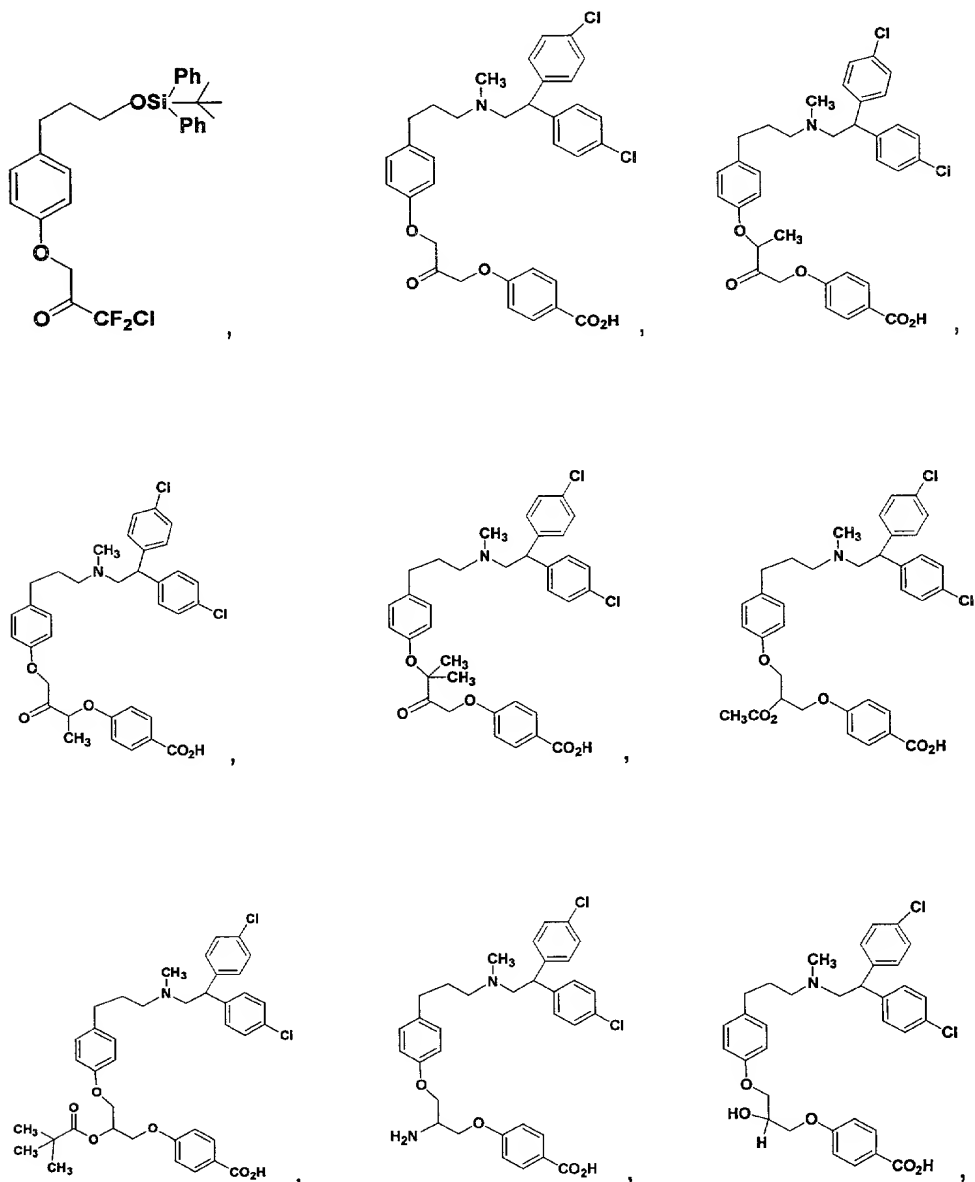
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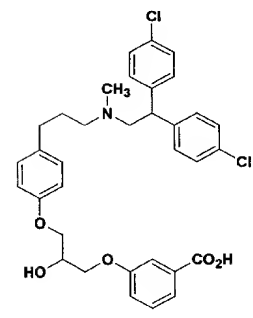
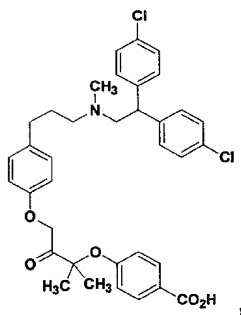
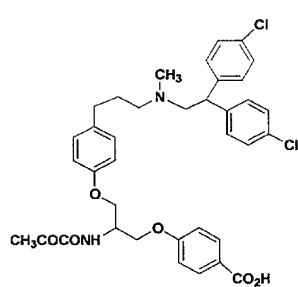
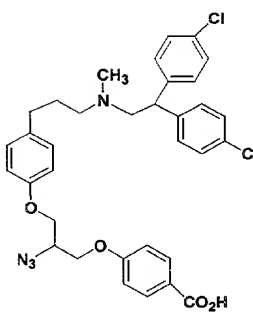
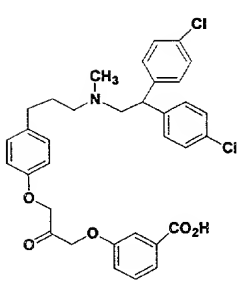
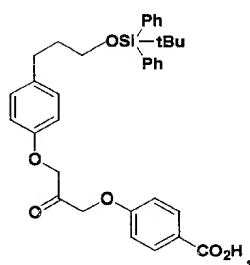
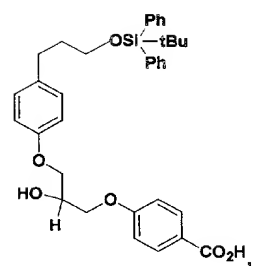
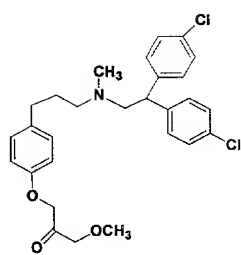
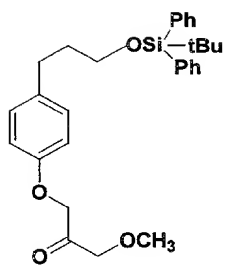


in which m and p each independently represent an integer of one to six,
 R^{15} , R^{16} , R^{17} are each independently C_1 – C_7 alkyl, R^{18} is C_1 – C_7 alkyl and

aryl represents  in which X^1 is halogen.

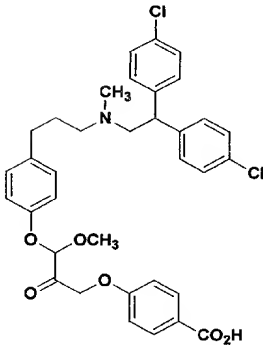
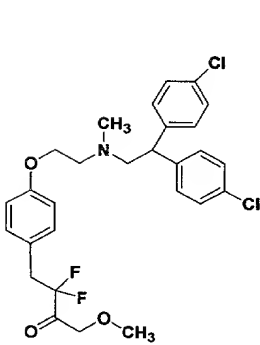
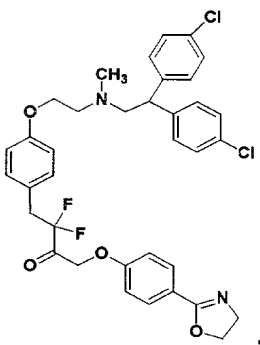
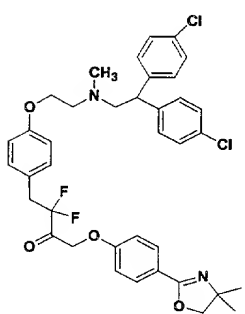
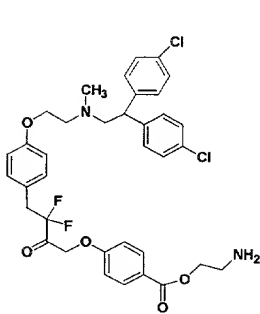
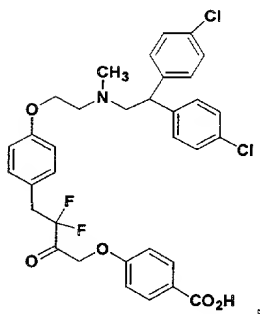
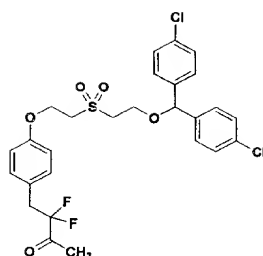
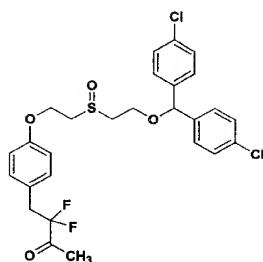
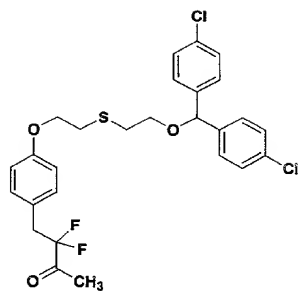
5 8. A compound selected from

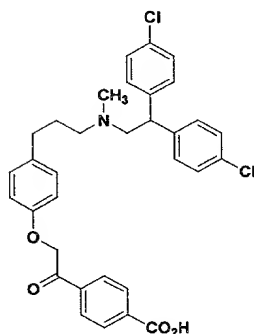




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9. A pharmaceutical composition for the inhibition of cytosolic
5 phospholipase A₂ comprising a therapeutically effective amount of a
compound of claim 1 and a pharmaceutically acceptable carrier.

10. A method of inhibiting cytosolic phospholipase A₂ in a mammal in need thereof, comprising administering to said mammal a therapeutically effective amount of a compound of claim 1.